53. (New) The method of claim 52, wherein the antibody is linked to a radioactive label, a fluorogenic label, a nuclear magnetic spin resonance label, biotin or an enzyme that generates a detectable product upon contact with a chromogenic substrate.

54. (New) The method of claim 52, wherein the antibody is linked to an alkaline phosphatase, hydrogen peroxidase or glucose oxidase enzyme.--

II. A RESPONSE TO THE OFFICE ACTION DATED MARCH 20, 2003

A. Status of the Claims

Claims 28-36 were pending upon the issuance of the Office Action dated March 20, 2003. Claim 28 has been amended, claims 30-36 have been deleted without prejudice or disclaimer and claims 37-54 have been added. Support for these amendments can be found in the claims as originally filed and throughout the specification. Attached as Appendix A is a copy of the amended claims with editing indicia and the newly added claims.

Therefore, claims 28-29 and 37-54 are currently pending. A clean copy of the currently pending claims is attached as Appendix B.

B. The Submission of Documents Not Considered By the Examiner

Applicant notes that the Examiner did not consider certain references listed in the Information Disclosure Statement ("IDS") filed with the U.S. Patent and Trademark Office on February 8, 2002. Based on the Action, Applicant believes that the references marked with a line through them by the Examiner are the references that were not considered. A copy of these references are submitted with this response for future consideration by the Examiner.

Applicant respectfully requests the Examiner to consider the enclosed references and make the appropriate notations (*i.e.* the Examiner's initials) next to the references listed in the IDS showing that such references have been considered.

Also, because these references were previously submitted in the parent application and are now missing from the file, Applicant respectfully requests that any future Action not be made final based on these references.

C. The Rejection of Claims 30-36 Under 35 U.S.C. § 101 Is Moot

The Action rejects claims 30-36 because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. Applicant notes that claims 30-36 have been cancelled without prejudice or disclaimer. As such, this rejection is rendered moot.

D. The Rejection of Claims 28, 30 and 33-36 Under 35 U.S.C. § 112, First Paragraph, Is Overcome

The Action rejects claims 28, 30 and 33-36 under 35 U.S.C. § 112, first paragraph, because the specification "does not reasonably provide enablement for an anti-phosphatidylserine antibody or method of making said antibody by administering a phosphatidylcholine/polypeptide conjugate." The Action, page 3.

Applicant traverses this rejection. Present claim 28 and newly added claims 37-54 are enabled by the present specification.

Applicant notes that all of the independent claims in this application are directed towards a method of making an antibody that specifically binds to phosphatidylserine "said method comprising administering to an animal a pharmaceutical composition comprising an immunologically effective amount of a phosphatidyl***serine***/polypeptide conjugate composition." See Appendix B, claims 28, 42 and 49(emphasis added). Applicant believes that the present claims satisfy the Action's concerns regarding enablement which are directed towards administering a phosphatidyl***serine***/polypeptide conjugate composition to make an antibody that specifically binds to phosphatidylserine.

Accordingly, Applicant requests that the rejection of claim 28 under 35 U.S.C. § 112, first paragraph, be withdrawn.

E. The Rejections of Claims 28-36 Under 35 U.S.C. § 102(b) Are Overcome

1. The Rejection of Claims 30-36 As Being Anticipated By Umeda *et al.* is Moot

The Action rejects claims 30-36 under 35 U.S.C § 102(b) as being anticipated by Umeda *et al.* Applicant notes that claims 30-36 have been cancelled without prejudice or disclaimer. Therefore, this rejection is rendered moot.

2. Claims 28-29 and 37-54 Are Not Anticipated By Bate *et al.*

i. Summary of the rejection and Applicant's claimed invention

The Action rejects claims 28-29 under 35 U.S.C § 102(b) as being anticipated by Bate *et al.* The Action states that Bate *et al.* teaches "a method of making an antibody that specifically binds to phosphatidylserine comprising administering to an animal a pharmaceutical composition comprising an immunologically effective amount of a phosphatidylserine/polypeptide conjugate wherein a composition comprising phosphatidylserine/KLH (PS-KLH) conjugate is administered to the animal (abstract)." The Action, page 6.

Applicant traverses this rejection. Claims 28-29 and newly added claim 37-54 are not anticipated by the Bate *et al.* reference.

Anticipation requires that each and every element of the claimed invention be described, either expressly or inherently, in a single prior art reference. *Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1327, 58 U.S.P.Q.2d 1545, 1552 (Fed. Cir. 2001); *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Thus, if even one element is missing in the cited reference(s), an anticipation rejection cannot be maintained.

Applicant presently claims "[a] method of making an antibody that ***specifically binds to phosphatidylserine***, said method comprising administering to an animal a pharmaceutical composition comprising an immunologically effective amount of a phosphatidylserine/polypeptide conjugate composition" (claim 28) (emphasis added). The antibody can be a ***monoclonal antibody*** (claims 41 and 49-54) (emphasis added). Applicant's claimed method can comprise "administering to an animal a pharmaceutical composition comprising an immunologically effective amount of a phosphatidylserine/polypeptide conjugate composition, wherein the phosphatidylserine/polypeptide conjugate composition ***is not a phosphatidylserine/KLH*** conjugate composition" (claim 42) (emphasis added).

As discussed in detail below, the Bate *et al.* reference does not administer a phosphatidylserine/polypeptide conjugate composition to an animal. Moreover, this reference does not teach or suggest a monoclonal antibody specific towards phosphatidylserine. Finally, it does not disclose phosphatidylserine/polypeptide conjugate compositions that are ***not*** phosphatidylserine/KLH conjugate compositions. Because of its deficient teachings, the Bate *et al.* reference cannot be said to anticipate the present claims, claims 28-29 and 37-54.

ii. The Bate et al. reference does not employ the use of phohsphatidylserine/polypeptide conjugate composition

The Bate *et al.* reference discloses a method of making a phospholipid/polypeptide conjugate by admixing phosphatidylserine and keyhole limpet haemocyanin ("KLH") with carbodiimide. *See* Bate *et al.*, page 139, column 2. An antisera is then produced by injecting the phospholipid/polypeptide conjugate composition into mice. *Id.*, page 140, column 1.

For reasons discussed in the following paragraphs, pending claims 28-29 and 37-54 are not anticipated by the disclosure of Bate *et al.* because this reference does not (1) administer a phosphatidylserine/polypeptide conjugate composition to an animal; and (2) disclose

phosphatidylserine specific antibodies. Applicant has provided herewith a Declaration of Alan J. Schroit ("Schroit Declaration") (attached as Appendix C) pursuant to 37 C.F.R. § 1.132 to support these arguments. Alan J. Schroit is an inventor for this application and has extensive experience in the field of cancer biology and phospholipid structures. Attached as Exhibit 1 is a copy of Dr. Schroit's *curriculum vitae.*

A person of skill in the art understands that "Phosphatidylserine is a phospholipid that has a free amine group located at the phosphate head portion of the phospholipid. It is this free amine group that distinguishes phosphatidylserine from other known phospholipids, such as phosphatidylcholine." Schroit Declaration, paragraph 5.

In producing the phospholipid/KLH conjugate disclosed in Bate *et al.*, the collaborators in this reference "coupled phosphatidylserine to KLH by mixing KLH and phosphatidylserine in the presence of carbodiimide." Schroit Declaration, paragraph 6; *see also* Bate *et al.*, page 139, column 2. A person of skill in the art recognizes that "This procedure couples KLH to the phosphate head portion of phosphatidylserine *via* the free amine group on phosphatidylserine. Because of this, the phosphatidylserine used in Bate *et al.* no longer has its distinguishing feature, the free amine group." Schroit Declaration, paragraph 6.

As such, "the coupling of KLH with phosphatidylserine *via* carbodiimide does not actually produce a phosphatidylserine/KLH conjugate. It follows, then, that the antibodies produced against the conjugated product in Bate *et al.* are not specific towards phosphatidylserine." Schroit Declaration, paragraph 7.

In contrast to Bate *et al.*, Applicant's claimed method comprises "administering to an animal a pharmaceutical composition comprising an immunologically effective amount of a phosphatidyl***serine***/polypeptide conjugate composition... ." See Appendix B, independent claims

28, 42 and 49. In fact, in a non-limiting example, the inventor made sure to "preserve the integrity of the lipids reactive serine headgroup" in producing its phosphatidylserine/polypeptide conjugates. *See* the specification, page 37, lines 23-30. Moreover, the resulting antibodies produced against the phosphatidylserine/polypeptide conjugate were assayed for their specificity towards phosphatidylserine. *Id.*, page 38, lines 12-15.

Because the phospholipid/KLH conjugate in Bate *et al.* is not a phosphatidylserine/KLH conjugate, the present anticipation rejection must fall. Moreover, because a non-phosphatidylserine/KLH conjugate was used to produce antisera in this reference, the resulting antibodies are not specific towards phosphatidylserine. Thus, present claims 28-29 and 37-54 are not anticipated by the Bate *et al.* reference.

Accordingly, Applicant respectfully requests that claims the rejection of claims 28-29 as being anticipated by Bate *et al.* be withdrawn.

iii. The Bate et al. reference does not teach or suggest a phosphatidylserine specific monoclonal antibody

Claims 41 and 49-54 are further patentable over the disclosure in Bate *et al.* because this reference does not disclose ***monoclonal*** antibodies specific towards phosphatidylserine. In Bate *et al.*, the collaborators produced antisera to a phospholipid/KLH conjugate[1] by injecting mice with the conjugate. *See* Bate *et al.*, page 140, column 1. Subsequently, the mice "were bled 12 days after the last injection." *Id.* A person of ordinary skill in the art would understand that this procedure does not produce monoclonal antibodies. *See, e.g.*, the specification, page 14, line 16 to page 15, line 10.

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[1] As discussed in the previous section, the phospholipid in the phospholipid/KLH conjugate in Bate *et al.* was not phosphatidylserine. Therefore, claims 41 and 49-54 are patentable over Bate *et al.* for at least the same reasons described above.

In contrast, claims 41 and 49-54 are specifically directed towards methods of producing monoclonal antibodies. Because Bate *et al.* does not teach or suggest the use of producing a monoclonal antibody, claims 41 and 49-54 are not anticipated over Bate *et al.*

iv. The Bate et al. reference does not teach or suggest the use of phosphatidylserine/non-KLH conjugates to produce phosphatidylserine specific antibodies

Claims 42-48 are further patentable over the disclosure in Bate *et al.* because this reference does not disclose the use of phosphatidylserine/non-KLH conjugates to produce phosphatidylserine specific antibodies. As discussed above, the only possible phosphatidylserine/polypeptide conjugate disclosed in Bate *et al.* is a phosphatidylserine/KLH conjugate. However, as explained above and in the Schroit Declaration, the end product of mixing KLH and phosphatidylserine did ***not*** produce a phosphatidylserine/KLH conjugate.

In contrast, Applicant claims "[a] method of making an antibody that specifically binds to phosphatidylserine, said method comprising administering to an animal a pharmaceutical composition comprising an immunologically effective amount of a phosphatidylserine/polypeptide conjugate composition, wherein the phosphatidylserine/polypeptide conjugate composition ***is not a phosphatidylserine/KLH*** conjugate composition." Because the Bate *et al.* reference does not teach or suggest a phosphatidylserine/non-KLH conjugate composition, it cannot be said that this reference anticipates claims 42-48.

F. Conclusion

Applicant believes this to be a full and complete response to the Office Action dated March 20, 2003. Applicant believes that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested.

Should the Examiner have any questions, comments, or suggestions relating to this case, the Examiner is invited to contact the undersigned Applicant's representative at (512) 536-3035.

Respectfully submitted,

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